REMARKS

Reconsideration of the present application in view of the following remarks is respectfully requested.

Status of the Claims

Claims 11-12, 16-21, 23, 25-30 and 32 were acted on by the Examiner in the Office Action dated July 6, 2006. Claims 19-22 are withdrawn from consideration. Claims 11, 12, 16-18, 23, 25-30 and 32 have been rejected. Accordingly, Claims 11, 12, 16-18, 23, 25-30 and 32 are presented for examination.

Summary of the Objections/Rejections

Claims 29, 30, and 32 have been rejected as non-enabling under 35 U.S.C. § 112, first paragraph. Claims 12, 16-18, 23, and 25-28 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Smith et al. (Gene Therapy 3:496-502, 1996). Claims 11-12, 16-18, and 25-28 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Trapnell et al. (WO 96/12406).

Section 112 Enablement Rejections of Claims 29, 30 and 32

Claims 29, 30, and 32 have been rejected as non-enabling under 35 U.S.C. § 112, first paragraph.

The Examiner asserts that the "specification does not provide any specific guidance on any method of using transgenic mammals cells in *ex vivo* gene therapy." In particular, the Examiner asserts that "neither the specification nor the art of record indicates that administering DSG will have any effect on transplants of transgenic autologous cells." Relying on two references, the Examiner asserts further that the art teaches that using transplants of transgenic autologous cells obviates immunological rejection and the use of immunosuppressants. Applicants traverse respectfully this rejection.

The Application Teaches an *Ex Vivo* Method

The M.P.E.P. § 2164.01 states that "whether a particular claim is supported by the disclosure in an application requires a determination of whether that disclosure, when filed, contained sufficient information regarding the subject matter of the claims as to enable one skilled in the pertinent art to make and use the claimed invention." Such is the case here.

As discussed in Applicants' Reply to the Action dated February 10, 2006, the specification describes an *ex vivo* administration of genetic material. For example, on page 4, lines 26-31 of the specification, applicants describe that "genetic material is inserted into cells *in vitro* or *in vivo* in the form of one or more nucleic acid chains. This is carried out, for example, with the aid of viral vectors, such as adenoviruses, retro viruses or herpesviruses, or other methods, for example, by means of transfection, by direct injection, by gene gun, or with the aid of liposomes, virosomes or receptor-mediated transport systems." (emphasis added). If the genetic material is inserted *in vitro* as described in the specification, then to get the genetic material into the mammal, an *ex vivo* method must be employed. Applicants have also provided publications which show that several *ex vivo* methods for administering gene therepy were known at the time the application was filed. See publications attached to applicants' Reply to the Action dated February 10, 2006.; see also the Raper et al. and Riper et al. publications cited by the Examiner. Moreover, the Examiner agrees that "using transplants of transgenic autologous cells was a well-known method at the time of filing." Accordingly, the Examiner has failed to sufficiently explain why he believes that one skilled in the art would not be able to perform applicants' claimed methods using an *ex vivo* procedure.

The Claimed Methods Are Operative and Useful

The Examiner seems to be asserting that the claim fails to meet the utility requirement under 35 U.S.C. § 101 because the claimed method is "nonuseful or inoperative" and, thus, the claims "necessarily fail to meet the how-to-use aspect of the enablement requirement of 35

U.S.C. § 112, first paragraph." M.P.E.P. § 2164.07. If this is the case, applicants traverse respectfully this rejection.

Relying on the Abstracts of Raper et al. (Cell Transplant 2:381-400, 1993) and Ridet et al. (Hum. Gene Ther. 10:271-280, 1999), the Examiner asserts that *ex vivo* gene therapy eliminates the risk of rejection and thus obviates the use of immunosuppressants. Applicants traverse respectfully. First, applicants note that the Raper et al. reference is less than emphatic on this point. On page 382, Raper et al. only suggests that by using autologous hepatocytes in an *ex vivo* method, "immunosuppression *may* not be required." (emphasis added). Second, the purpose of the invention is to increase the tolerance of a mammal to *transgenic cells* not just the viral vector. As discussed below, this is also a difference over the Smith et al. and Trapnell et al. publications. Accordingly, for purposes of applicants' claimed method, it does not make a difference whether those cells are transfected *in vivo* or *in vitro*.

Furthermore, applicants disagree respectfully with the Examiner's assertion that *ex vivo* gene therapy eliminates the risk of rejection and thus obviates the use of immunosuppressants. As explained in the specification, in addition to viral vectors being subject to the immune response, the transgenic cells themselves frequently produce an immunological reaction *in vivo*.

> It is known that the insertion of genetic material into cells of a mammal, of man or even of various animals such as horses, sheep, cows, goats, pigs, dogs, mice or rats frequently produces an immunological reaction in vivo. Thus the *transgenic cells* are killed, for example, by cytotoxic immune cells and thus the expression of one or more proteins or peptides effected by means of the inserted genetic material is ended by this cellular immune reaction.

Specification at page 1, lines 11-22 (emphasis added). Applicants' experimental results support these statements. For example, the results show clearly and definitively a marked increase in the production of a reporter gene (human alpha-1 antitrypsin) in a mouse after a single administration of a viral vector carrying that gene by administering an immunosuppressant. Even 15 days after the administration of the immunosuppressant was stopped, the reporter gene showed a marked increase in expression. See Table 1 on page 10. Because human alpha-1

antitrypsin is not antigenic in mice, the immunosuppressant was able to markedly increase the expression by suppressing the immune response against the transgenic cells. Because applicants' method suppresses the cellular immune response directed to the transgenic cells, applicants' method is equally operative and useful in an *ex vivo* method where the cells are transformed outside the mammal.

Accordingly, applicants request respectfully withdrawal of the enablement rejection.

Section 103(a) Obviousness Rejections

Claims 12, 16-18, 23, and 25-28 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Smith et al. (Gene Therapy 3:496-502, 1996). Claims 11, 12, 16-18, and 25-28 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Trapnell et al. (WO 96/12406). Because these references do not teach or suggest all the elements of the claims, the claims are non-obvious and should be allowed.

The Examiner asserts that "based on the guidance provided by either Smith et al. or Trapnell et al. that administration of DSG at the time of adenoviral vector delivery prevented the formation of anti-adenovirus neutralizing antibodies, and the knowledge in the art that administration of adenovirus vectors frequently induces a neutralizing antibody response that can decrease the efficacy of adenoviral gene delivery, it would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made to modify the teachings of Smith et al. or Trapnell et al. by administering a single dose of an adenoviral vector with DSG."

Applicants respectfully traverse this rejection as the Examiner has not established a *prima facie* case of obviousness. "To establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation

of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations." MPEP § 2143.

Smith et al. and Trapnell et al.

Smith et al. and Trapnell et al. disclose essentially the same methods. For example, compare Figure 2(b) of Smith et al. with Figure 17 of Trapnell et al. Both publications are directed to a method of administering adenovirus vectors expressing a transgene along with administration of an immunosuppressant that will decrease the formation of anti-adenovirus neturalizing antibodies to allow for a more effective second administration of the adenovirus vector. The goal of Smith et al. and Trapnell et al. is to decrease the humoral immune response to the adenoviral vectors to allow for *repeat* doses of the vector. For example, Smith et al. explicitly states that its goal is to increase the tolerance to multiple repeat doses of a vector.

> In present study we demonstrate that the humoral immune response to a systemically administered adenovirus vector is dose dependent and can be modulated by a brief treatment with the immunosuppressive agents cyclophosphamide or deosyspergualin at the time of initial treatment. This strategy permits effective *multiple repeat* doses of a vector encoding a therapeutic gene . . . . Smith et al., p. 496 (emphasis added).

Similarly, Trapnell et al. states that the object of their invention is "to provide for sustained efficacy of gene transfer via *repeated administration of adenoviral vectors*, and for sustained expression of the transferred gene, through the suppression of an immune response against the adenoviral vectors." Trapnell et al., p. 4 (emphasis added). Accordingly, Trapnell et al. and Smith et al. are focused on the transient expression of the transgenic product. This is reflected in the fact that both Trapnell et al. and Smith et al. test only for the expression of transgenic product a week after the repeat administration of the vector. Smith et al., captions to Fig. 1, 2(b); Trapnell et al. at p. 36. Trapnell et al. and Smith et al. do not test for long term expression of the transgenic product because they are primarily concerned with the humoral immune response against the viral vector to allow for repeated dosing of the vector.

Applicants' independent claims (claims 16 and 26) distinguish over the disclosure of each

of these references in reciting "a single administration of a vector."

Applicants' Invention

In contrast to Smith et al. and Trapnell et al., applicants' invention is directed to increasing tolerance to the transgenic cells by suppression of the cellular immune response. Specification at p. 4, lines 5-6. More particularly, the object of applicants' invention is to "prevent the rapid destruction of the transgenic cells and thus increase the tolerance of a mammal to transgenic cells. Thus, the expression of the transgenic product is maintained longer in vivo. As a consequence, "*repeated administration of the genetic material could be stopped . . . .*" Specification at p. 2, lines 6-10 (emphasis added). In Example 2, applicants show that for at least a period of 200 days following administration of the vector, production of the transgenic product is at least 50% higher than the control. Accordingly, an embodiment of applicants' invention is a method of increasing the tolerance to transgenic cells and a method for increasing expression of a transgenic product using a *single* administration of a vector carrying a transgene.

Neither Smith et al. nor Trapnell et al. disclose a single administration of a vector

The Examiner admits that neither Trapnell et al. nor Smith et al. disclose using only a single administration of a vector to increase tolerance to transgenic cells or for producing transgenic product. See Office Action at page 6-7. Moreover, when considered in their entirety, Trapnell et al. and Smith et al. teach away from applicants' invention as the object of both Trapnell et al. and Smith et al. is to allow for effective *repeated administration* of a vector.

Modifying Trapnell et al. or Smith et al. Improperly Modifies their Operation

MPEP § 2143.01 provides that "if the proposed modification . . . of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims *prima facie* obvious. *In re Ratti*, 270 F.2d 810, 123 USPQ 349 (CCPA 1959)."

Here, the principle of operation of both Smith et al. and Trapnell et al. is to allow for the repeated administration of viral vectors. See Smith et al., p. 496 ("This strategy permits effective multiple repeat doses of a vector encoding a therapeutic gene . . . ."); Trapnell et al., p. 4 ("It is therefore an object of the present invention to provide for sustained efficacy of gene transfer via repeated administration of adenoviral vectors . . . ."). Smith et al. and Trapnell et al. teach that the immunosuppressant is only needed if a repeated dose of the adenoviral vector is given. For example, figure 2(b) of Smith et al. and figure 17 of Trapnell et al. show that the administration of a single dose (i.e., no prior doses) of the adenoviral vector without an immunosuppressant (bar A) results in an expression level of the encoded gene that is higher than the expression level from a repeated dose of the adenoviral vector with DSG (bar D). The purpose of Smith et al. and Trapnell et al. is to avoid the result in bar B of Figure 2(b) of Smith et al. or Figure 17 of Trapnell et al. by administering an immunosuppressant so that a repeated dose of a viral vector as in bar D results in substantial expression of the encoded gene. Thus, one of skill in the art would thus not be motivated to modify the teachings of Smith et al. or Trapnell et al. by administering a single dose of an adenoviral vector with an immunosuppressant because Smith et al. and Trapnell et al. teach that a single dose of a viral vector would not benefit from administration of an immunosuppressant.

Conversely, applicants have shown that the administration of an immunosuppressant even with a single administration of an adenoviral vector results in a prolonged increased expression of the encoded gene as compared to a single administration of an adenoviral vector without an immunosuppressant. See Table 1 on page 10 (DSG versus Control).

Accordingly, the obviousness rejections should be withdrawn.

Conclusion

In view of the proposed claim amendments and the arguments presented above, the present application is believed to be in condition for allowance and an early notice thereof is

earnestly solicited. The Office is invited to contact the undersigned counsel in order to further the prosecution of this application in any way.

Respectfully submitted,

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